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REVIEW ARTICLE

Proton pump inhibitors and the risk of severe adverse events – A cardiovascular bombshell?☆

Nelson Cunha[a,*], **António Pedro Machado**[b]

[a] *Serviço de Cardiologia, Hospital Universitário de Santa Maria (CHLN), Centro Académico de Medicina de Lisboa e CCUL, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal*
[b] *Serviço de Medicina I B, CHLN - Hospital de Santa Maria, Lisboa, Portugal*

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Abstract Proton pump inhibitors are currently one of the most prescribed pharmacological classes in developed countries, given their effectiveness and safety profile, which has until now been considered favorable.

However, in recent years, several papers have been published that associate prolonged use of these drugs with a wide range of adverse effects, posing doubts about their safety. Among the adverse effects described is an increased risk of cardiovascular events. This relationship was first described in subjects after acute coronary syndrome due to the interference of proton pump inhibitors in the cytochrome P450 2C19 and the conversion of clopidogrel to its active metabolite. More recent studies have also reported this relationship with the use of antiplatelet agents that do not depend on cytochrome P450 2C19 activation. The proposed mechanism is inhibition of dimethylarginine dimethylaminohydrolase, a physiological inhibitor of asymmetric dimethylarginine, which increases plasma concentrations of the latter enzyme, leading to lower levels of nitric oxide.

By reviewing in this article the relationship between the use of proton pump inhibitors and increased risk of cardiovascular and cerebrovascular events, the authors aim to alert the medical community to the potentially harmful effects of these drugs, and recommend the setting of a moratorium on their prolonged use.

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* Corresponding author.
E-mail address: nelsoncunha@campus.ul.pt (N. Cunha).

PALAVRAS-CHAVE
Inibidores da bomba de protões;
Óxido nítrico;
Síndrome coronária aguda;
Acidente vascular cerebral

Inibidores da bomba de protões e o risco de eventos adversos graves – uma bomba cardiovascular?

Resumo Os inibidores da bomba de protões são atualmente uma das classes farmacológicas mais prescritas nos países desenvolvidos, dada a sua eficácia e perfil de segurança até então considerado favorável.

Contudo ao longo dos últimos anos, têm sido publicados vários trabalhos que associam o uso prolongado destes fármacos a uma panóplia de efeitos adversos, colocando dúvidas acerca da sua segurança. Entre os efeitos adversos descritos, salienta-se o aumento do risco de eventos cardiovasculares. Esta relação foi primeiramente descrita nos indivíduos após síndrome coronária aguda pela interferência dos inibidores da bomba de protões no citocromo P450 2C19 e a conversão do clopidogrel em metabolito ativo. No entanto, trabalhos mais recentes descrevem esta relação também com o uso de antiagregantes que não dependem da ativação pelo citocromo P450 2C19. O mecanismo proposto é pela inibição da dimetilarginina dimetilaminohidrolase, inibidor fisiológico da dimetilarginina assimétrica, aumentando assim as concentrações plasmáticas desta última enzima e por sua vez traduzindo-se em níveis mais reduzidos de óxido nítrico.

Os autores ao rever neste artigo a relação entre o uso de inibidores da bomba de protões e o risco acrescido de eventos cardio e cerebrovasculares, pretendem alertar a comunidade científica para os potenciais efeitos nefastos destes fármacos e recomendam a colocação de uma moratória à sua utilização prolongada.

Introduction

Proton pump inhibitors (PPIs) were the sixth most prescribed pharmacological class in Portugal in 2015, with 6.99 million units sold, and the eighth in value (41.2 million euros at wholesale prices), according to data from Statistics Portugal, the national statistics institute.

Factors contributing to this high consumption include these drugs' efficacy in treating dyspepsia, peptic ulcer, gastroesophageal reflux disease and erosive esophagitis, a safety profile that has been considered favorable, the fall in prices as generic versions entered the market, inappropriate prescribing and use for periods exceeding those recommended, and rebound acid hypersecretion.[1–3]

The rebound effect, in which dyspepsia recurs after withdrawal of treatment, and which leads to dependence, is one of the main reasons for chronic use of PPIs in a large and growing number of patients. Paradoxically, the drugs induce the symptoms they are supposed to treat.[4]

The development of dependence may explain the results of a study in the UK showing that the total volume of PPIs prescribed rose tenfold in four years, with repeat prescriptions accounting for 77% of the total in the last year analyzed.[5] In a US study, PPIs were prescribed appropriately in only 35% of cases; they were prescribed for gastroprotection in 18% and in 36% there was no documented appropriate indication.[6]

PPIs cause hypergastrinemia and achlorhydria. In the short term, hypergastrinemia leads to hyperacidity, worsening the symptoms of gastroesophageal reflux and dyspepsia, when treatment is withdrawn.[3,7] In the long term, it can result in enterochromaffin-like cell hyperplasia and parietal cell hypertrophy, leading to dyspepsia and increasing the risk of carcinoid tumors.[8]

Despite the widely held favorable opinion of the safety of PPIs, results published in recent years have raised serious questions concerning their prolonged use. A growing number of studies and editorials have begun to call attention to the association between PPI use and increased risk for a variety of conditions. These include *Clostridium difficile*-associated diarrhea and enteric infection with *Campylobacter*, *Salmonella*, *Shigella* and *Listeria*[9–11]; community-acquired pneumonia[12–14]; bone fractures, particularly with very long treatment periods[15–17]; dose-dependent increases in extrahepatic cholangiocarcinoma and carcinoma of the ampulla of Vater, duodenum, jejunum and pancreas[18–20]; esophageal adenocarcinoma in individuals with Barrett's esophagus[21]; acute interstitial nephritis[22] and chronic kidney disease[23]; and atherothrombotic cardiovascular events.[24,25]

Proton pump inhibitors and risk of cardiovascular events

The first reports of an increased risk of cardiovascular events associated with PPIs came from studies on patients with a history of acute coronary syndrome treated with clopidogrel. These studies initially attributed this rise in rates of reinfarction and other acute coronary events after hospital discharge to the reduction in clopidogrel's antiplatelet effect caused by the PPI interfering in its conversion in the

liver to the active metabolite by blocking the cytochrome P450 2C19 (CYP2C19).[26,27]

In view of the controversy surrounding these early studies, a systematic review and meta-analysis[28] was performed examining only studies published between 2012 and 2016. This confirmed that the concomitant use of clopidogrel and PPIs following coronary angioplasty was associated with higher short-term mortality and a higher long-term incidence of major adverse cardiac events, myocardial infarction and stent thrombosis, although long-term mortality was not significantly different.

However, other recent studies have associated PPIs not only with worse clinical outcomes when used concomitantly with clopidogrel in high cardiovascular risk populations, but also with reduced therapeutic benefit for other antiplatelet agents, such as aspirin and ticagrelor, which do not involve activation of the CYP2C19 isoenzyme, suggesting that another mechanism is at work.[29–31] This appears to be corroborated by other studies showing that all members of the PPI pharmacological class, even those with a minimal effect on CYP2C19, increase cardiovascular risk in patients with acute coronary syndrome.[24,26,30,32–34]

Various groups have suggested that this increased risk is mainly due to reduced endothelial production of nitric oxide (NO), which functions as an endogenous platelet inhibitor. Thus, the effect of PPIs on platelet aggregation would result from their deleterious effect on endothelial function.[35]

NO released by endothelial cells plays a crucial role in vascular homeostasis, acting as an endogenous vasodilator regulating local vascular tone, as an endogenous platelet inhibitor regulating platelet activity, and through its antiatherogenic action on the endothelium, maintaining the normal structure of the vessel wall.[36]

NO synthesis in vessels is regulated by endothelial NO synthase,[37] which is inhibited by ADMA (asymmetric dimethylarginine), such that higher levels of ADMA reduce endothelial NO production.[38]

Plasma ADMA concentrations are elevated in renal failure, coronary disease, hypertension, diabetes and pre-eclampsia. When patients with these conditions take PPIs, ADMA levels in endothelial cells rise even more, further inhibiting NO synthase, reducing endothelial NO production and exacerbating endothelial dysfunction. As the bioavailability of NO diminishes, conditions favor the progression of atherosclerosis and the occurrence of atherothrombotic events.[25,39]

PPIs increase plasma ADMA levels and reduce endothelial NO production by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that degrades ADMA.[40] The research group that identified this cascade reported that in the same preclinical study ADMA levels rose by around 30% in ex-vivo human endothelial cells exposed to a PPI and in-vivo serum concentrations rose by about 20% in mice receiving a PPI.[40]

The same group recently performed a prospective crossover pilot study in 21 individuals (11 healthy and 10 with established cardiovascular disease) to assess in vivo the correlation in humans between PPI use and ADMA levels and endothelial function. Although PPI use did not significantly influence vascular endothelial function, higher ADMA levels were observed in the PPI arm, and this trend was more pronounced among subjects with a history of vascular disease.[41]

However, this study has some methodological flaws, particularly the short treatment period (four weeks in each group) and the small sample size, which would be unlikely to provide results with statistical significance. Furthermore, the EndoPAT technique used in the study to assess the effect of drugs on vascular function is not the ideal test to detect variations in endothelial function in the early stages of clinical drug trials,[42] and the alterations identified by this method may be partly NO-dependent.[43] The study has other limitations that are beyond the scope of this review. Even so, since there is a tendency for higher ADMA levels with PPI use, there appears to be a need for studies with more representative populations and longer follow-up, in order to obtain results with clinical significance.

As stated above, it is known that elevated plasma ADMA levels are a risk factor for cardiovascular morbidity and mortality, in both patients with cardiovascular disease and apparently healthy individuals.[44–50] The latter association is thus a potentially serious public health problem that should be investigated.

On the assumption that PPIs can increase levels of ADMA even in healthy individuals, it is essential to assess the relationship between PPI use and the risk of a first cardiovascular event in the population without known cardiovascular disease.

The volume of studies published on this subject has increased markedly in recent years. Examining the association between PPI monotherapy and cardiovascular events in individuals with no history of cardiovascular disease, Sun et al.[51] performed a meta-analysis of 16 randomized controlled trials including 7540 individuals on PPI monotherapy for gastroesophageal reflux disease. The results show a 70% increased cardiovascular risk in patients taking PPIs (relative risk 1.70, 95% confidence interval [CI] 1.13-2.56, p=0.01, I^2=0%), an association that appeared to be stronger in the omeprazole and long-term treatment subgroups.

There have been few studies on the association between PPI use and cardiovascular events that included stroke in the combined endpoints[24,30,31,52–55] and only one assessed recurrent stroke as its primary endpoint. Wang et al. accordingly performed a retrospective analysis based on a nationwide database to assess the relation between risk of a first ischemic cerebrovascular event and PPI use in the Taiwanese population. They compared hospitalizations with a primary diagnosis of ischemic stroke in individuals with and without current PPI use at a 1:1 ratio. PPI use was associated with a higher risk of a first ischemic stroke, independently of antiplatelet therapy, with a hazard ratio of 1.36 (95% CI 1.14-1.620, p=0.001). The association was stronger in patients aged <60 years.[56]

Conclusion

On the basis of the results of the above studies, which suggest a causal relation between PPI use and increased risk of cardiovascular events, enteric infections, pneumonia, chronic kidney disease and cancer, among others, the

authors recommend at least the setting of a moratorium on their prolonged use.

Wider awareness of these worrying data on the safety of long-term PPI use should prompt discussion of their use (and abuse) in Portugal, and help bring about more rational prescribing of these drugs.

Conflicts of interest

The authors have no conflicts of interest to declare.

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